Serum Interleukin-18 Levels Are Associated With Nephropathy and Atherosclerosis in Japanese Patients With Type 2 Diabetes

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OBJECTIVE — Interleukin (IL)-18 is a proinflammatory cytokine secreted from mononuclear cells. Serum concentration of IL-18 is a strong predictor of death in patients with cardiovascular diseases. Recent studies have shown that microinflammation is involved in the pathogenesis of diabetic nephropathy as well as of cardiovascular diseases. This study aimed to test the hypothesis that the serum level of IL-18 is a common predictor of nephropathy and atherosclerosis in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Eighty-two Japanese patients with type 2 diabetes and 55 age- and sex-matched healthy control subjects were enrolled. Patients with renal dysfunction (creatinine clearance <1 ml/s) were excluded. We assessed clinical parameters and measured serum and urinary IL-18 levels, serum IL-6 levels, carotid intima-media thickness (IMT), and brachial-ankle pulse wave velocity (baPWV) in all patients. Further, we evaluated changes of urinary albumin excretion rate (AER) after 6 months in 76 diabetic patients.

RESULTS — Serum and urinary IL-18 levels were significantly elevated in patients with type 2 diabetes as compared with control subjects (serum IL-18 179 ± 62 vs. 121 ± 55 pg/ml, $P < 0.001$; urinary IL-18 97 ± 159 vs. 47 ± 54 pg/ml, $P = 0.035$). Univariate linear regression analysis showed significant positive correlations between serum IL-18 and AER (r [correlation coefficient] = 0.525, $P < 0.001$), HbA_{1c} ($r = 0.242$, $P = 0.029$), high-sensitivity C-reactive protein (hs-CRP) ($r = 0.240$, $P = 0.031$), and urinary β-2 microglobulin ($r = 0.235$, $P = 0.036$). Serum IL-18 levels also correlated positively with carotid IMT ($r = 0.225$, $P = 0.042$) and baPWV ($r = 0.232$, $P = 0.040$). We also found a significant correlation between urinary IL-18 and AER ($r = 0.309$, $P = 0.005$). Multivariate linear regression analysis showed that AER (standard correlation coefficients [B] = 0.405, $P < 0.001$) and hs-CRP ($B = 0.207$, $P = 0.033$) were independently associated with serum IL-18 levels. AER was also independently associated with urinary IL-18 levels ($B = 0.295$, $P = 0.005$). Moreover, serum and urinary IL-18 levels correlated positively with AER after 6 months ($r = 0.489$, $P < 0.001$ and $r = 0.320$, $P = 0.005$) and changes in AER during the follow-up period ($r = 0.268$, $P = 0.018$ and $r = 0.234$, $P = 0.042$).

CONCLUSIONS — Serum levels of IL-18 might be a predictor of progression of diabetic nephropathy as well as cardiovascular diseases.

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Abbreviations: ACEI, ACE inhibitor; AER, albumin excretion rate; ARB, angiotensin II type 1 receptor blocker; baPWV, brachial-ankle pulse wave velocity; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; ICAM, intercellular adhesion molecule; IL, interleukin; IMT, intima-media thickness; SBP, systolic blood pressure; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Low-grade inflammation (microinflammation) occurs in diabetic patients as well as those with cardiovascular diseases (1,2). Several reports indicate that high-sensitivity C-reactive protein (hs-CRP) (3) and proinflammatory cytokines such as interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α, and IL-18 are elevated in patients with type 2 diabetes (4–7). The mechanisms for elevation of serum IL-18 levels in type 2 diabetes remain unclear, although oxidative stress is a candidate (8). Activation of nuclear factor-κB through oxidative stress induced by hyperglycemia increases concentrations of circulating proinflammatory cytokines (2).

High serum IL-18 concentrations have recently been identified as a strong predictor of death in patients with coronary artery disease (9) and acute ischemic stroke (10). A major mechanism of cardiovascular events mediated by IL-18 is decreased stability of plaque. Carotid intima-media thickness (IMT) measured by carotid ultrasound is a useful tool for assessing cardiovascular diseases in diabetes (11), and a clinical study demonstrated that carotid IMT in patients with high IL-18 shows a greater thickness than in patients with normal IL-18 (12).

Microalbuminuria is a predictor of cardiovascular and renal risk in diabetes (13) and nondiabetes (13,14). Patients with diabetic nephropathy, especially in the context of type 2 diabetes, have a high incidence of cardiovascular disease, which leads to increased mortality (15). Indeed, worldwide, diabetic nephropathy is the major reason for dialysis, and survival of type 2 diabetes undergoing dialysis therapy is very poor due to cardiovascular events. However, the precise mechanisms underlying the relationship between microalbuminuria and cardiovascular disease remain unclear.

Recent studies, including ours, suggest that an inflammatory mechanism mediated by macrophages may play important roles in the pathogenesis of diabetic nephropathy. We previously demonstrated that the intercellular adhesion

molecule (ICAM)-1 is upregulated and mediates infiltration of macrophages in kidneys of patients with diabetic nephropathy and in diabetic animals (16–18). Moreover, we have reported that ICAM-1–deficient mice are resistant to renal injuries after induction of diabetes, suggesting that inflammatory processes contribute to the development of diabetic nephropathy. IL-18 is a proinflammatory cytokine produced from activated macrophages. Recently, serum IL-18 levels have been reported elevated in patients with diabetic nephropathy (19). IL-18 is known to lead to production of other proinflammatory cytokines (20), endothelial apoptosis (21), upregulation of ICAM-1 (22), and hyperhomocysteinemia (12). Thus, IL-18 might be an important factor not only in the process of atherosclerosis but also in the development and progression of diabetic nephropathy.

This study aims to investigate whether serum and urinary IL-18 levels are predictors of diabetic nephropathy as well as of atherosclerosis in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— A total of 82 patients (48 females and 34 males) with type 2 diabetes who had been referred to the diabetes outpatient department at the Okayama Saiseikai General Hospital were enrolled. The diagnosis of type 2 diabetes was made in accordance to the criteria of the World Health Organization. All patients who fulfilled the following inclusion criteria were considered for the study: no episodes of ketoacidosis, initial diagnosis of diabetes at >40 years of age, no demonstrable antibodies to GAD and renal dysfunction (creatinine clearance <1.00 ml/s). Age was 62.5 ± 7.5 years and diabetes duration 10.8 ± 6.3 years (means ± SD). BMI was 23.8 ± 3.0 kg/m^2. Past history of cardiovascular disease was defined as a clinical attack of stroke, ischemic heart disease, and arteriosclerosis obliterance.

Venous blood and urine were obtained in the early morning after an overnight fast. Urinary albumin excretion rate (AER) was measured with an immunoturbidimetric assay Micro Alb (Nitto Boseki, Tokyo, Japan). Normoalbuminuria was defined as AER <30 mg/gCr (n = 41), microalbuminuria as AER 30–299 mg/gCr (n = 31), and macroalbuminuria as AER >300 mg/gCr (n = 10).

Thirty-two patients received insulin therapy, 49 received oral antidiabetic agents, and 9 received only diet therapy. Twenty-two patients had hypertension, defined as systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg or, alternatively, as having treatment with one or more antihypertensive agents. The latter included ACE inhibitor (ACEI) or angiotensin II type 1 receptor blocker (ARB) (n = 34), combination therapy with ACEI and ARB (n = 7), and statins (n = 20). No patients included in this study received hormone replacement therapy.

As control subjects, 55 nondiabetic subjects (32 females and 23 males), without any medical treatment, were selected to match the overall age and sex distribution of the patients with type 2 diabetes. The control subjects also fulfilled the following inclusion criteria: normal blood pressure (SBP <140 mmHg and DBP <90 mmHg), normal glucose tolerance (fasting plasma glucose <6.11 mmol/l and HbA_{1c} (A1C) <5.8%), AER <30 mg/gCr, creatinine clearance >1.00 ml/s, no clinical history of cardiovascular disease, and no symptoms of acute inflammatory disease. The mean age of healthy control subjects was 59.5 ± 8.7 years. Informed consent was obtained from all participants, and the study was approved by the ethical committee of Okayama Saiseikai General Hospital.

Measurement of serum and urinary levels of IL-18 and serum levels of hs-CRP and IL-6

Serum levels of hs-CRP were measured using an immunonephelometric assay kit (Dade Behring, Marburg, Germany). Serum levels of IL-6 were measured using a chemiluminescent enzyme assay (CLEIA kit; Fujirebio, Tokyo, Japan). Serum and urinary IL-18 levels were measured using a commercially available enzyme-linked immunosorbent assay (MBL, Nagoya, Japan). Urinary IL-18 levels were divided by urinary creatinine levels (pg/mlCr).

Measurements of carotid IMT and brachial-ankle pulse wave velocity

IMT of the common carotid artery was determined using duplex ultrasonography with a 7.5-MHz linear transducer (SSD-5500; Aloka, Tokyo, Japan). Carotid IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second on a sonographic image. Measurements of IMT were made at each of the three sites of the greatest thickness on both sides. Carotid IMT was defined as the mean of these maximal IMT measurements. SBP and DBP were measured twice with the patient in a sitting position after 5 min rest. ABI-form (BP-203RPE II; Nippon Colin, Komaki, Japan) allows an automated multiple pulse wave measurement and was used to measure left and right brachial-ankle pulse wave velocity (baPWV). A trained physician at our institution performed all scans. In this study, the highest values of SBP, DBP, IMT, and baPWV from the left and the right sides were used for the evaluation of each patient.

AER follow-up after 6 months

After the initial assessment of baseline AER (pre-AER), measurement of AER was repeated after 6 months in patients continuing with the same treatment during follow-up. AER after 6 months (post-AER) and changes in AER over the 6 months (post-AER–to–pre-AER ratio) were assessed.

Statistics

Statistical analyses were performed with the SPSS for Windows statistical software system. Data are presented as means ± SD or actual numbers. Variables of serum or urinary IL-18 levels, serum IL-6 levels, hs-CRP, pre-AER, post-AER, and post-AER–to–pre-AER ratio did not show a Gaussian distribution (Shapiro-Wilks test), and natural logarithmic transformation was used to render the distribution of these variables normal (ln). Comparisons of data between control subjects and patients with type 2 diabetes were analyzed by Student's unpaired t test or χ^2 test for sex (female). Correlation was determined by univariate or multivariate linear regression analysis. Differences between mean in pre- and post-AER were assessed with Student's paired t test. A P value <0.05 was accepted as indicating statistical significance.

RESULTS

Association of serum and urinary IL-18 levels with clinical data

Characteristics of control subjects and patients with type 2 diabetes and univariate analysis of relationships between serum or urinary IL-18 and characteristics of patients with type 2 diabetes are shown in Table 1. Serum IL-18 levels, urinary IL-18 levels, and serum IL-6 levels were significantly higher in patients with type 2 diabetes than in age- and sex-matched control subjects (serum IL-18 179 ± 62

Table 1—*Characteristics of control and type 2 diabetic subjects, and univariate analysis of relationships between logarithmic serum or urinary IL-18 levels and characteristics of type 2 diabetes*

				(ln)serum IL-18		(ln)urinary IL-18	
	Control subjects	Type 2 diabetic subjects	*P**	*r*	*P*	*r*	*P*
n	55	82					
Sex (female) (*n*)	32	48	0.076	0.175	0.123	0.255	0.022†
Age (years)	59.5 ± 8.7	62.5 ± 7.5	0.054	−0.172	0.118	0.152	0.117
Duration of diabetes (years)	—	10.8 ± 6.3	—	0.120	0.282	0.073	0.517
History of cardiovascular events (yes) (*n*)	—	17	—	0.174	0.117	0.136	0.229
BMI (kg/m^2)	22.4 ± 2.5	23.8 ± 3.0	0.005‡	0.142	0.204	−0.130	0.251
SBP (mmHg)	124 ± 14	131 ± 16	0.004‡	0.147	0.187	0.011	0.925
DBP (mmHg)	75 ± 10	77 ± 10	0.215	0.140	0.208	−0.920	0.418
Total cholesterol (mmol/l)	5.59 ± 0.98	5.28 ± 0.80	0.044†	−0.025	0.824	0.088	0.437
HDL cholesterol (mmol/l)	1.60 ± 0.44	1.34 ± 0.41	0.001‡	−0.138	0.218	0.041	0.718
LDL cholesterol (mmol/1)	3.31 ± 0.85	3.21 ± 0.75	0.428	−0.060	0.590	0.123	0.275
Lipoprotein-α (g/l)	0.25 ± 0.20	0.22 ± 0.18	0.478	−0.460	0.687	0.076	0.515
Fasting plasma glucose (mmol/l)	5.47 ± 0.51	8.44 ± 3.28	<0.001§	0.213	0.055	−0.018	0.877
A1C (%)	5.1 ± 0.5	7.3 ± 1.1	<0.001§	0.242	0.029†	0.128	0.259
Creatinine clearance (ml/s)	1.55 ± 0.37	1.53 ± 0.49	0.766	0.097	0.384	−0.003	0.982
Serum β-2 microglobulin (μg/ml)	1.66 ± 0.28	1.83 ± 0.47	0.022†	0.088	0.435	−0.017	0.883
Urinary β-2 microglobulin (μg/ml)	0.06 ± 0.07	0.14 ± 0.20	0.009‡	0.235	0.036†	0.136	0.233
Fibrinogen (g/l)	2.85 ± 0.61	3.00 ± 0.53	0.144	0.054	0.630	0.172	0.130
AER (mg/gCr)	8 ± 7	103 ± 432	—	—	—	—	—
(ln)AER (1n[mg/gCr])	1.85 ± 0.74	2.91 ± 1.55	<0.001§	0.525	<0.001§	0.309	0.005‡
hs-CRP (mg/l)	1.02 ± 3.24	1.05 ± 1.43	—	—	—	—	—
(ln)hs-CRP (1n[mg/l])	−0.93 ± 1.12	−0.45 ± 0.97	0.009‡	0.240	0.031†	0.087	0.441
Patient with ACEI or ARB (yes) (*n*)	—	34	—	0.227	0.041†	−0.031	0.782
Patient with statins (yes) (*n*)	—	20	—	0.275	0.021†	−0.028	0.804
Carotid IMT (mm)	0.70 ± 0.14	0.86 ± 0.18	<0.001§	0.225	0.042†	0.034	0.768
baPWV (m/s)	14.2 ± 3.5	17.1 ± 3.4	<0.001§	0.232	0.040†	0.208	0.068
Serum IL-6 (pg/ml)	1.50 ± 1.24	1.95 ± 1.16	—	—	—	—	—
(ln)serum IL-6 (1n[pg/ml])	0.20 ± 0.62	0.49 ± 0.60	0.006‡	0.032	0.779	0.029	0.798
Serum IL-18 (pg/ml)	121 ± 55	179 ± 62	—	—	—	—	—
(ln)serum IL-18 (1n[pg/ml])	4.69 ± 0.48	5.14 ± 0.34	<0.001§	—	—	−0.019	0.866
Urinary IL-18 (pg/mlCr)	47 ± 54	97 ± 159	—	—	—	—	—
(ln)urinary IL-18 (1n[pg/mlCr])	3.28 ± 1.11	5.14 ± 0.34	0.035†	−0.019	0.866	—	—

Data are means ± SD. **P* for type 2 diabetic versus control subjects. †$P < 0.05$; ‡$P < 0.01$; §$P < 0.001$. *r*, correlation coefficient.

vs. 121 ± 55 pg/ml, $P < 0.001$; urinary IL-18 97 ± 159 vs. 47 ± 54 pg/ml, $P = 0.035$; IL-6 1.95 ± 1.16 vs. 1.50 ± 1.24 pg/ml, $P = 0.006$; age 62.5 ± 7.5 vs. 59.5 ± 8.7 years, $P = 0.054$). By univariate linear regression analysis, we found a significant correlation between serum IL-18 and A1C (*r* [correlation coefficient] = 0.242, $P = 0.029$), urinary β-2 microglobulin ($r = 0.235$, $P = 0.036$), patients with ACEI or ARB (yes; $r = 0.227$, $P = 0.041$), patients with statins (yes; $r = 0.275$, $P = 0.021$), urinary AER ($r = 0.525$, $P < 0.001$), or hs-CRP ($r = 0.240$, $P = 0.031$) in patients with type 2 diabetes. On the other hand, we found no significant correlation between serum IL-18 levels and A1C, urinary β-2 microglobulin, or hs-CRP in control subjects. Moreover, we found a significant correlation between urinary IL-18 and sex (female: $r = 0.255$, $P = 0.022$) or AER ($r = 0.309$, $P = 0.005$) in patients with type 2 diabetes. However, we found no significant correlation between serum IL-18 levels and urinary IL-18 levels or serum IL-6 levels in control subjects and in patients with type 2 diabetes.

Independent factors of serum and urinary IL-18 levels in patients with type 2 diabetes

We next performed multivariate linear regression analysis for factors significantly correlated with serum and urinary IL-18 levels (Table 2). AER (standard correlation coefficients [*B*] = 0.405, $P < 0.001$) and hs-CRP ($B = 207$, $P = 0.033$) were independently associated with serum IL-18 levels. AER was also independently associated with urinary IL-18 levels ($B = 0.295$, $P = 0.005$).

Association of serum and urinary IL-18 levels with parameters of atherosclerosis

We performed univariate analysis of the relationships between the parameters of atherosclerosis and IL-18 levels in patients with type 2 diabetes (Table 1). Serum IL-18 levels correlated positively with carotid IMT and baPWV ($r = 0.225$, $P = 0.042$ and $r = 0.232$, $P = 0.040$). Urinary IL-18 levels were not related to IMT and baPWV. We also found no significant correlation between serum IL-18 levels and carotid IMT or baPWV in control subjects.

Table 2—*Multivariate analysis of relationships between logarithmic serum or urinary IL-18 levels and characteristics of type 2 diabetes*

Variables	*B*	*P*
Dependent variable: (ln)serum IL-18, $R^2 = 0.378$, $P < 0.001$		
Independent variable		
(ln)AER	0.405	<0.001
(ln)hs-CRP	0.207	0.033
Patient with statins (yes)	0.158	0.108
Urinary β-2 microglobulin	0.157	0.118
A1C	0.114	0.242
Patient with ACEI or ARB (yes)	0.021	0.838
Dependent variable: (ln)urinary IL-18, $R^2 = 0.138$, $P = 0.003$		
Independent variable		
(ln)AER	0.295	0.005
Sex (female)	0.208	0.053

B, standard correlation coefficients; R^2, multiple coefficients of determination.

Relationships between serum or urinary IL-18 levels and AER after 6 months or changes in AER during the follow-up period

During the following-up period, two patients dropped out and four (two with hyperglycemia, two with cardiovascular disease) were admitted to hospitals. Consequently, post-AER was assessed in 76 patients (Fig. 1). Pre-AER in 76 patients was 107 ± 440 mg/gCr [(ln)pre-AER 3.03 ± 1.55 (ln)mg/gCr]. Changes in AER were revealed as post-AER–to–pre-AER ratio. The mean of AER showed no significant change during the follow-up period [post-AER 151 ± 601 mg/gCr, (ln) post-AER 3.03 ± 1.71 (ln)mg/gCr, $P = 0.958$]. Serum and urinary IL-18 levels correlated positively with post-AER ($r = 0.489$, $P < 0.001$ and $r = 0.320$, $P = 0.005$). Moreover, serum and urinary IL-18 levels correlated positively with the post-AER–to–pre-AER ratio ($r = 0.268$, $P = 0.018$ and $r = 0.234$, $P = 0.042$).

CONCLUSIONS — In the present study, we found that serum IL-18 levels were closely correlated with AER as well as with carotid IMT and baPWV in patients with type 2 diabetes. AER was an independent determinant of serum and urinary IL-18 levels. Moreover, serum and urinary IL-18 levels correlated positively with AER after 6 months and changes in AER during the follow-up period. These results provide the first evidence of a close association of serum and urinary IL-18 levels with AER. The serum IL-18 level might be a predictor not only of cardiovascular diseases but also of diabetic nephropathy in patients with type 2 diabetes.

A1C and hs-CRP were also positively correlated with serum IL-18 levels, with hs-CRP being an independent determinant of serum IL-18 levels. However, there was no significant correlation between serum IL-18 and serum IL-6 levels. In our present study, serum IL-6 levels were not correlated with AER. While there have been several studies suggesting that IL-6 is involved in the pathogenesis of diabetic nephropathy in vivo and in vitro (23–26), Moriwaki et al. (19) reported that serum IL-18 and tumor necrosis factor (TNF)-α levels were significantly elevated in diabetic patients with microalbunimuria as compared with normoalbuminuria, whereas serum IL-6 levels were not elevated in diabetic patients with microalbuminuria. It remains unclear why we could not find an association of serum IL-6 levels with AER; however, it is possible that serum levels of IL-6 are less sensitive to renal injury than urinary IL-6 levels. Absence of a correlation between serum IL-18 and IL-6 levels might indicate that IL-18 is involved in the pathogenesis of diabetic nephropathy through a different mechanism than IL-6.

The close correlation between serum and urinary IL-18 levels and AER strongly suggest a relationship between low-grade inflammation and albuminuria in patients with type 2 diabetes, as recently described (15,27). IL-18 is a potent proinflammatory cytokine that induces interferon-γ (28), which in turn induces functional chemokine receptor expressions in human mesangial cells (29). Furthermore, IL-18 leads to production of other proinflammatory molecules, including IL-8, IL-1β, TNF-α, and intercellular adhesion molecule-1 (20,22), from mononuclear cells and macrophages. These molecules are known to increase in type 2 diabetes

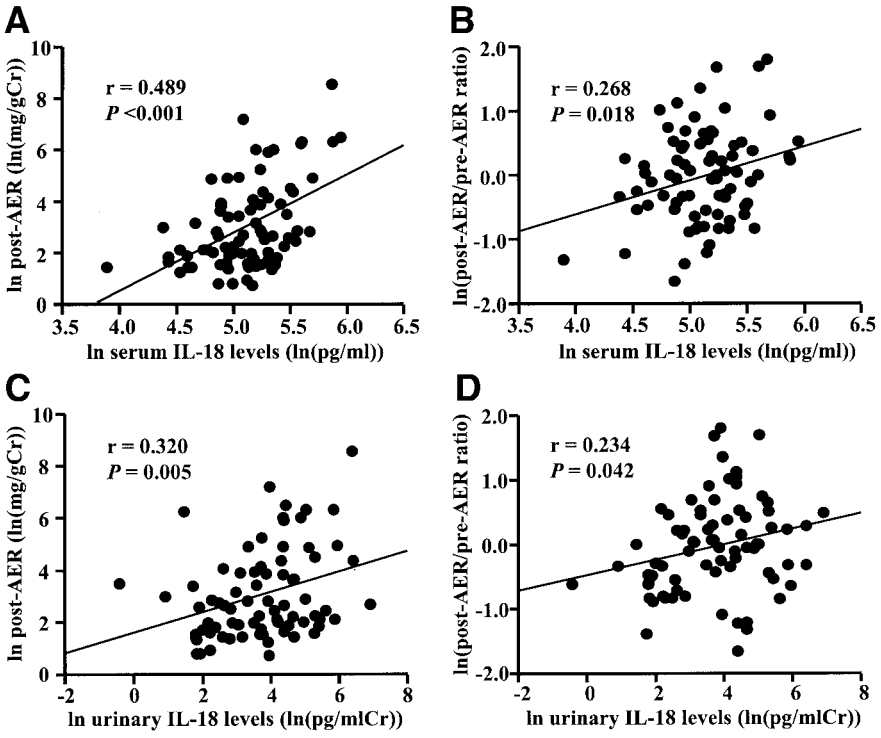

Figure 1—*Serum* (A, B) *and urinary* (C, D) *IL-18 levels correlate positively with post-AER or post-AER–to–pre-AER ratio. Variables of serum or urinary IL-18 levels, post-AER, and the post-AER–to–pre-AER ratio were naturally transformed logarithmically.*

(4,5,30) and may contribute to maintain microinflammation in renal tissues of patients with type 2 diabetes.

Microalbuminuria, hs-CRP, and other proinflammatory markers are known to be associated with cardiovascular diseases. In the present study, we also found that serum IL-18 levels were positively correlated with carotid IMT and baPWV in patients with type 2 diabetes. Several studies have reported that carotid IMT (11,12) and baPWV (31) are useful markers for evaluation of atherosclerosis in type 2 diabetes. A clinical study reported that decrease in glomerular filtration rate is linked to atherosclerosis (32). We showed that urinary β-2 microglobulin, a marker for tubulo-interstitial injuries, is positively correlated with serum IL-18 levels. Recently, several studies have demonstrated that proximal tubular cells are potential sources of IL-18 as well as monocytes/macrophages and T cells in ischemic acute tubular necrosis in mice (33,34). Thus, increase in serum IL-18 levels might be provoked by tubulo-interstitial injuries in patients with diabetic nephropathy.

We assessed the changes of AER at 6 months to test the hypothesis that the IL-18 level is a predictor of the progression of diabetic nephropathy in patients with type 2 diabetes. Serum and urinary IL-18 levels correlated positively with AER after 6 months and with changes in AER during the follow-up period. These results suggest that elevation of serum and urinary IL-18 levels may be a risk factor for development of diabetic nephropathy. In our study, 34 patients were prescribed an ACEI or ARB. Some studies have reported that angiotensin II blockade reduced production of inflammation molecules, including CRP (35), TNF-α, and IL-18 (36). ARBs suppress the expansion of reactive oxygen species generation and nuclear factor-κB with decreasing concentration of CRP (35). ACEIs inhibit lipopolysaccharide-induced production of TNF-α, IL-1β, IL-10, IL-12, and IL-18 in human monocyte-derived dendritic cells (36). Contrary to these reports, Tan et al. (37) report that ARB reduces AER in diabetic nephropathy with no significant change of hs-CRP. On the other hand, statins are known to have anti-inflammatory effects independent of their lipid-lowering effect (38). However, patients with ACEI/ARB or statins were positively correlated with serum IL-18 levels in our study. The mechanism underlying these discrepancies remains unclear, although patients with higher AER might have been administered these drugs. Because a cross-sectional study is not suitable to assess the effects of drugs, a prospective study will be required to resolve this question.

In the present study, we showed cross-sectional data associated with serum or urinary IL-18 levels. This makes it difficult to prove causal relationships. Prospective studies or in vitro studies are needed to clarify the causal relationships between IL-18 and both atherosclerosis and diabetic nephropathy in patients with type 2 diabetes.

In conclusion, the present results indicate that serum and urinary IL-18 levels are elevated and closely correlated with AER in patients with type 2 diabetes. Serum IL-18 levels may be a predictor of the progression of diabetic nephropathy as well as of cardiovascular diseases. Moreover, IL-18 might be a crucial molecule that connects albuminuria and cardiovascular disease in patients with type 2 diabetes.

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